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1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/829,388	ROSSI ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-116* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-116* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Prior to setting forth the Restriction Requirement, it is pointed out that applicants have presented the instant claims in improper format (e.g., see claim 21). The claims are improperly joined as the various groups indicated below appear to encompass distinct methods of therapy and diagnosis to such an extent that they are considered separately patentable. A method of diagnosing requires a detection step wherein a detectable label is identified or visualized, which is not required by the method of treating. Claim 21 does not require this "detection step" and is not a proper process claim. Therefore, the restriction will be set forth for each of the various groups, irrespectively of the improper format of the claims, because these are not proper process claims.

2. If applicant elects one of the inventions of Groups 106-108, 118-123, 130 or 131, further election is required under 35 U.S.C. 121 (see item nos. 4-8 below).

Election/Restrictions

3. Restriction to one of the following inventions is required under 35 U.S.C. 121:

1. Claims 1, 5 and 8-12 drawn to a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody) wherein each antigen binding site of the polyvalent protein complex has a different binding specificity, classified in class 530, subclass 387.3.

2-46. Claims 1-4, 6-7, 14-20 drawn to a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody)

wherein the polyvalent protein complex binds a single distinct tumor associated antigen (see claim 17), classified in class 530, subclass 388.8. *If Applicant elects one of inventions 2-46, applicant is required to clearly identify a single elected distinct tumor associated antigen of claim 17 for examination.*

47. Claims 21-29 drawn to a pretargeting method of diagnosing a neoplastic condition comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a tumor associated antigen and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 7.1.

48. Claims 21 and 28-38 drawn to a pretargeting method of treating a neoplastic condition comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a tumor associated antigen and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a

bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 133.1.

49-93. Claims 39-40 drawn to a method of treating a neoplastic disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein the polyvalent protein complex binds a tumor associated antigen (see claim 39), classified in class 424, subclass 156.1, for example. *If Applicant elects one of inventions 49-93, applicant is required to clearly identify the single distinct tumor associated antigen of claim 39 for examination.*

94. Claims 41-49, drawn to a method for treating a B cell malignancy in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD19, classified in class 424, subclass 143.1.

95. Claims 41-49, drawn to a method for treating a B cell malignancy in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD20, classified in class 424, subclass 144.1.

96. Claims 41-49, drawn to a method for treating a B cell malignancy in a subject comprising administering a polyvalent protein complex comprising

two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD22, classified in class 424, subclass 152.1.

97. Claims 41-49, drawn to a method for treating a B-cell immune or autoimmune disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD19, classified in class 424, subclass 130.1.

98. Claims 41-49, drawn to a method for treating a B-cell immune or autoimmune disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD20, classified in class 424, subclass 136.1.

99. Claims 41-49, drawn to a method for treating a B-cell immune or autoimmune disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD22, classified in class 424, subclass 141.1.

100. Claims 50-54, drawn to a method for detecting/diagnosing a B cell malignancy in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding

sites, wherein each antigen binding site binds a distinct epitope of CD19, classified in class 435, subclass 7.2.

101. Claims 50-54, drawn to a method for detecting/diagnosing a B cell malignancy in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD20, classified in class 435, subclass 7.23.

102. Claims 50-54, drawn to a method for detecting/diagnosing a B cell malignancy in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD22, classified in class 435, subclass 7.92.

103. Claims 50-54, drawn to a method for detecting/diagnosing a B-cell immune or autoimmune disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD19, classified in class 435, subclass 7.24.

104. Claims 50-54, drawn to a method for detecting/diagnosing a B-cell immune or autoimmune disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD20, classified in class 435, subclass 7.72.

105. Claims 50-54, drawn to a method for detecting/diagnosing a B-cell immune or autoimmune disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD22, classified in class 435, subclass 7.94.

106. Claims 56-57 and 72-79 drawn to a method of diagnosing a disease caused by a fungus comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 341.

107. Claims 58-59 and 72-79 drawn to a method of diagnosing a disease caused by a virus comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 339.

108. Claims 60-61 and 72-79 drawn to a method of diagnosing a disease caused by a bacterium comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 340.

109. Claim 62 and 72-79 drawn to a method of diagnosing a disease caused by a mycoplasma comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 340.

110. Claim 63 and 72-79 drawn to a method of diagnosing a disease caused by a parasite comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 342.

111. Claim 64 and 72-79 drawn to a method of diagnosing malaria comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 342.

112. Claims 65-66 and 72-79 drawn to a method of diagnosing an autoimmune disease comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 343.1.

113. Claim 67 and 72-79 drawn to a method of diagnosing myocardial infarction, ischemic heart disease, or atherosclerotic plaques comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 337.

114. Claim 68 and 72-79 drawn to a method of diagnosing graft rejection comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 343.2.

115. Claim 69 and 72-79 drawn to a method of diagnosing Alzheimer's disease comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 336.

116. Claim 70 and 72-79 drawn to a method of diagnosing a disease caused by atopic tissue comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 334.

117. Claims 71-79 drawn to a method of diagnosing inflammation caused by accretion of activated granulocytes, monocytes, lymphoid cells, macrophages or an infectious agent comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 335.

118. Claims 81-82 and 97-104 drawn to a pretargeting method of diagnosing a non-neoplastic disease caused by a fungus comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 341.

119. Claims 81-82 drawn to a pretargeting method of treating a non-neoplastic disease caused by a fungus comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 136.1.

120. Claims 83-84 and 97-104 drawn to a pretargeting method of diagnosing a non-neoplastic disease caused by a virus comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 339.

121. Claims 83-84 drawn to a pretargeting method of treating a non-neoplastic disease caused by a virus comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a

marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 147.1.

122. Claims 85-86 and 97-104 drawn to a pretargeting method of diagnosing a non-neoplastic disease caused by a bacterium comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 340.

123. Claims 85-86 drawn to a pretargeting method of treating a non-neoplastic disease caused by a bacterium comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct

comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 150.1.

124. Claim 87 and 97-104 drawn to a pretargeting method of diagnosing a non-neoplastic disease caused by a mycoplasma comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 340.

125. Claim 87 drawn to a pretargeting method of treating a non-neoplastic disease caused by a mycoplasma comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 168.1.

126. Claim 88 and 97-104 drawn to a pretargeting method of diagnosing a non-neoplastic disease caused by a parasite comprising administering a

polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 342.

127. Claim 88 drawn to a pretargeting method of treating a non-neoplastic disease caused by a parasite comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 151.1.

128. Claim 89 and 97-104 drawn to a pretargeting method of diagnosing malaria in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering

a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 342.

129. Claim 89 drawn to a pretargeting method of treating malaria in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 151.1.

130. Claims 90-91 and 97-104 drawn to a pretargeting method of diagnosing an autoimmune disease comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 343.1.

131. Claims 90-91 drawn to a pretargeting method of treating an autoimmune disease comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 153.1.

132. Claim 92 and 97-104 drawn to a pretargeting method of diagnosing myocardial infarction, ischemic heart disease, or atherosclerotic plaques comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 337.

133. Claim 92 drawn to a pretargeting method of treating myocardial infarction, ischemic heart disease, or atherosclerotic plaques comprising administering a polyvalent protein complex comprising two polypeptides

and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 145.1.

134. Claim 93 and 97-104 drawn to a pretargeting method of diagnosing graft rejection comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 343.2.

135. Claim 93 drawn to a pretargeting method of treating graft rejection comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent,

and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 154.1.

136. Claim 94 and 97-104 drawn to a pretargeting method of diagnosing Alzheimer's disease comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 336.

137. Claim 94 drawn to a pretargeting method of treating Alzheimer's disease comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 146.1.

138. Claim 95 and 97-104 drawn to a pretargeting method of diagnosing a disease caused by atopic tissue comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 334.

139. Claim 95 drawn to a pretargeting method of treating a disease caused by atopic tissue comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 143.1.

140. Claim 96-104 drawn to a pretargeting method of diagnosing inflammation caused by accretion of activated granulocytes, monocytes, lymphoid cells, macrophages or an infectious agent comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen

binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents, classified in class 435, subclass 335.

141. Claim 96 drawn to a pretargeting method of treating inflammation caused by accretion of activated granulocytes, monocytes, lymphoid cells, macrophages or an infectious agent comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents, classified in class 424, subclass 158.1.

142. Claim 105 drawn to a method of antibody dependent enzyme prodrug therapy (ADEPT) comprising administering to a patient with a neoplastic disorder a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein said complex comprises a covalently attached enzyme capable of activating a prodrug, optionally

administering a clearing agent, and administering said prodrug to the patient, classified in class 424, subclass 175.1.

143. Claims 106-107 drawn to a method of detection/staining a target molecule/cell using one or more polyvalent protein complex(es) comprising two polypeptides and at least three antigen binding sites, classified in class 435, subclass 172.1.

144. Claims 108-109 drawn to a nucleic acid encoding a first or second polypeptide of a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites and an expression cassette comprising said nucleic acid, classified in class 536, subclass 23.53.

145. Claims 110-116 drawn to an episome, host cells and a method of preparing a polyvalent protein complex wherein said episome comprises a first promoter operably linked to a first nucleic acid molecule encoding a polypeptide comprising three immunoglobulin variable domains and a second promoter operably linked to a second nucleic acid molecule encoding a polypeptide comprising three immunoglobulin variable domains, wherein the encoded polypeptides form a complex comprising three antigen binding sites, classified in class 435, subclass 320.1.

4. This application contains claims directed to the following patentably distinct species of the claimed invention:

5. If one of the inventions of Groups 106, 118 or 119 is elected, Applicant is required under 35 U.S.C. 121 to further elect a single disclosed species in claim 57 or 82 for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 56 and 81 are generic.

6. If one of the inventions of Groups 107, 120 or 121 is elected, Applicant is required under 35 U.S.C. 121 to further elect a single disclosed species in claim 59 or 84 for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 58 and 83 are generic.

7. If one of the inventions of Groups 108, 122 or 123 is elected, Applicant is required under 35 U.S.C. 121 to further elect a single disclosed species in claim 61 or 86 for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 60 and 85 are generic.

8. If one of the inventions of Groups 112, 130 or 131 is elected, Applicant is required under 35 U.S.C. 121 to further elect a single disclosed species in claim 66 or 91 for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 65 and 90 are generic.

The species are distinct in having different etiologies, effects and therapeutic endpoints.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim

is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

9. Claim 13 links inventions 2-46. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim, claim 13.

10. Claim 55 links inventions 106-117. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim, claim 55.

11. Claim 80 links inventions 118-141. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim, claim 80. Upon the indication of allowability of the linking claim, the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring

all the limitations of the allowable linking claim will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104. Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

12. The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups 1-46, 144 and 145 represent separate and distinct products, which are made by materially different methods, and are used in materially different methods, which have different modes of operation, different functions and different effects. The polyvalent protein complex of Group 1, the polyvalent protein complexes of Groups 2-46, the polynucleic acids of Groups 144-145 are all structurally and chemically different from each other. The polynucleotide is made by nucleic acid synthesis, while the antibodies of the polyvalent protein complexes are raised by immunization. Furthermore, the polynucleotide can be used for hybridization screening

and the polyvalent protein complexes can be used to purify the respective antigens, for examples. The polyvalent protein complex of Group I comprises at least three antigen binding sites wherein each antigen binding site has a different binding specificity, which is not required by any of the other Groups. The polyvalent protein complexes of Groups 2-46 comprise two antigen binding sites that bind a tumor associated antigen and a targetable construct, wherein each of the inventions of Groups 2-46 binds a different tumor associated antigen, which are not required one fro the other and are patentably distinct. The examination of all groups would require different searches in the U.S. Patent shoes and the scientific literature and would require the consideration of different patentability issues. Thus, the inventions of Groups 1-46, 144 and 145 are patentably distinct.

The methods of Inventions 47-143 differ in the method objectives, method steps and parameters and in the reagents used. Invention 47 recites a pretargeting method of diagnosing a neoplastic condition comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a tumor associated antigen and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents; Invention 48 recites a pretargeting method of treating a neoplastic condition comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are

specific for a tumor associated antigen and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents; Inventions 49-93 recites a method of treating a neoplastic disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein the polyvalent protein complex binds a tumor associated antigen; Inventions 94-96 recite a method for treating a B cell malignancy in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD19, CD20 and CD22, respectively; Inventions 97-99 recite a method for treating a B cell immune or autoimmune disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD19, CD20 and CD22, respectively; Inventions 100-102 recite methods for detecting/diagnosing a B cell malignancy in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD19, CD20 and CD22, respectively; Inventions 103-105 recite methods for detecting/diagnosing a B cell immune or autoimmune disorder in a subject comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein each antigen binding site binds a distinct epitope of CD19, CD20 and CD22,

respectively; Inventions 106-117 recite methods of diagnosing a disease caused by various organisms/conditions comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites; Inventions 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138 and 140 recite pretargeting methods of diagnosing a non-neoplastic disease caused by various organisms/conditions comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more diagnostic agents; Inventions 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139 and 141 recite pretargeting methods of treating a non-neoplastic disease caused by various organisms/conditions comprising administering a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites (i.e., triabody), wherein two antigen binding sites are specific for a marker specific for the disease and one antigen binding site is directed to a targetable construct comprising a bivalent hapten, optionally administering a clearing agent, and administering said targetable construct comprising a bivalent hapten which further comprises one or more therapeutic agents; Invention 142 recites a method of antibody dependent enzyme prodrug therapy (ADEPT) comprising administering to a patient with a neoplastic disorder a polyvalent protein complex comprising two polypeptides and at least three antigen binding sites, wherein said complex comprises a covalently attached

enzyme capable of activating a prodrug, optionally administering a clearing agent; Invention 143 recites a method of detection/staining a target molecule/cell using one or more polyvalent protein complex(es) comprising two polypeptides and at least three antigen binding sites. The examination of all groups would require different searches in the U.S. Patent shoes and the scientific literature and would require the consideration of different patentability issues. Thus, inventions 47-143 are separate and distinct in having different method objectives, method steps, parameters, reagents used and different endpoints and are patentably distinct.

Inventions 1 and 94-99 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the polyvalent protein complex of Group I can be used in a materially different method such as immunodiagnosis as in Groups 100-105 in addition to the materially different therapeutic methods of Groups 94-99, for examples.

Inventions 2 and 47 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the polyvalent protein complex of Group 2 can be used in a materially different method such as cancer

immunotherapy of group 48 in addition to the materially different diagnostic method of Group 47.

13. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

14. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain

dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder.

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

15. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(l).

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827